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Pulmonary fibrosis in systemic sclerosis: Diagnosis & management

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A B S T R A C T

Systemic sclerosis is a fascinating, although uncommon condition. However, fibrosing alveolitis in systemic sclerosis patients is common and is associated with significant morbidity and mortality. Investigations assist, not only with diagnosis, but also with assessment of disease severity and assessment of the likelihood of disease progression, thus helping to identify those requiring closer medical supervision. Treatment of fibrosing alveolitis in systemic sclerosis is complex, as the risks of some therapies may outweigh the potential benefits, and for those with advanced disease there is a lack of donor organs available for transplantation. Great strides continue to be made in unravelling the mysteries of the immunopathogenesis of fibrosing alveolitis in systemic sclerosis, and this should eventually lead to the development of more rational and targeted pharmacological therapies.

Educational aims

- To discuss the clinical presentation of FASSc.
- To discuss the physiology of FASSc and testing for the disorder.
- To outline radiology of FASSc in detecting subtle abnormalities.
- Look into further treatments of the disorder.

1. Introduction

Systemic sclerosis (SSc) or scleroderma is a connective tissue disorder (CTD) characterised by skin thickening, which may be accompanied by involvement of internal organs. SSc may affect the lungs by fibrosing alveolitis (FA or FASSc); pulmonary hypertension (PHT); lung cancer; pleural disease; aspiration pneumonitis; extrathoracic restriction through a "cuirasse effect"; diffuse alveolar damage and pulmonary haemorrhage.

The term systemic sclerosis is derived from Greek (sclero = hard, derma = skin). SSc has a female preponderance of 4:1, which in the childbearing years may be as high as 15:1, with a peak age of incidence of 30–50 years.[1] On the basis of the distribution of skin involvement SSc is divided into limited (lSSc) and diffuse (dSSc) cutaneous subtypes,[2] with the limited form not extending proximal to either the elbows or the knees, although facial skin thickening occurs in both. The limited form includes the CREST syndrome (**C**alcinosis, **R**aynaud's phenomenon, o**E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasia). This division into subtypes has important connotations with respect to autoantibody profile and spectrum of internal organ involvement.

2. Clinical features of FASSc

Assessment of exercise tolerance on both flat and stairs is important, as is whether the patient is limited by breathlessness or because of some other symptom (s) e.g. joint pains. Joint pains may mask respiratory symptoms, as the patient cannot exercise sufficiently to precipitate breathlessness.

Dyspnoea is a common symptom of FASSc, initially exertional but with disease progression the patient may become breathless at rest. Cough in FASSc may be dry or productive.[3] Haemoptysis is uncommon in FASSc and should alert the clinician to the possibility of scar malignancy, which may occur in up to 3% of SSc patients and is associated with the presence of FASSc.[4] Haemoptysis can also occur from endobronchial telangiectasia.

The commonest physical finding in FASSc is bilateral basal crackles.[5] Digital clubbing is uncommon, possibly as a result of impaired peripheral blood flow in SSc and skin tightening.[6] Features of pulmonary hypertension may be present (raised jugular venous pressure [JVP], loud pulmonary 2nd heart sound [P2], pedal oedema and a right ventricular/parasternal heave). Pulmonary arterial hypertension (PAH) has a prevalence of 21% in lSSc and 26% in dSSc.[7] Whilst this may be hypoxaemia-induced, due to disease severity, it may well be because of pulmonary vascular disease (PVD), *per se*, particularly in lSSc (10% of lSSc cases)[8] and if the patient is anti-centromere antibody positive (*vide infra*). The prevalence of isolated PAH in patients with dSSc is 2%.[8] Furthermore, the prevalence of PAH appears to be no different in SSc

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patients with (18%) and without (22%) FASSc.[9] The extent and severity of cutaneous and pulmonary involvement do not correlate very well but FASSc is more common in dSSc, and PHT in lSSc.[10]

3. Autoantibodies in SSc

Anti-nuclear antibodies (ANA) are autoantibodies directed against structures within cell nuclei. They may be detected at different dilutions, with the more CTD-specific values (>1:100) being found in <10% of the normal population[11] with a nucleolar pattern suggesting SSc.[1]

Approximately half of patients with SSc carry an autoantibody, either anti-topoisomerase-I (26%) or anti-centromere antibody (ACA [22%]), with no patient carrying both autoantibodies.[12] Anti-topoisomerase-I is associated with diffuse cutaneous disease and FASSc[12–14] whereas ACA is associated with limited cutaneous disease and pulmonary hypertension.[13,14]

4. Physiology

4.1. Pulmonary function tests

The classical PFT abnormalities seen in FASSc include a *restrictive ventilatory defect associated with a depressed gas transfer (TLCO)[3,31]. Lung volumes may give an indication of fibrosis severity but with co-existent emphysema, they may be relatively normal because of gas trapping. TLCO can be up to 20% less (on % predicted) than lung volumes but further, more disparate, loss of TLCO raises the possibility of co-existent pulmonary vascular disease (PVD).

*Restrictive ventilatory defect is characterised by a reduction total lung capacity (TLC), forced expiratory volume in 1 s *(FEV_1) and forced vital capacity (FVC) with an elevated FEV_1: FVC ratio.[32,33]

A single PFT result gives a snapshot of disease extent but, in order to get a view of disease activity, serial testing is required as subtle downward trends may be revealed, which may reflect disease activity. Decreases of <10% may be reassessed at a 3-month interval to see if this is the start of a trend downwards. Wells et al.[34] showed that the major determinant of functional impairment is the degree of FA on high resolution computed tomography (HRCT), and that this is best reflected in the percent predicted TLCO.

4.2. Six minute walk test

The six minute walk test (6MWT) is highly reproducible in FASSc but its use in FASSc is limited by its weak correlation with % predicted FVC and Borg dyspnoea index and a non-correlation with % predicted gas transfer.[35] However, this study used the 6MWT outcome measure as distance walked rather than oxygen desaturation. Others have shown that oxygen desaturation of >4% is associated with % predicted FVC < 80%.[36]

5. Radiology

5.1. Chest radiography

The chest radiograph (CXR) in FASSc is abnormal in up to 80% of cases (i.e. it can appear normal)[37,38] and fibrosis on the CXR may predate the onset of scleroderma.[39] Typical CXR features include a predominantly bibasal reticulonodular pattern. Cystic areas may form within fibrotic areas giving a "honeycomb" appearance. Fibrosis may result in elevation of the hemidiaphragms and decreased lung volumes. Pneumothoraces may result from rupture of subpleural cysts.[40] Oesophageal dilatation may be seen on CXR but is better visualised with HRCT and has been found in 80% of asymptomatic cases on HRCT.[41]

Using the CXR to assess disease activity may lead to delays in detecting clinically significant disease as it is less sensitive than other methods such as CT for detecting subtle abnormalities.

5.2. High resolution computed tomography

HRCT is a major advance in the management of FASSc and may obviate the need for confirmatory histology.

Each CT image is a 2-dimensional image of the thorax in cross-section and is a matrix of picture elements (pixels), each of which is a 3-dimensional entity (voxel) with volume.[42] The thicker the sections, the thicker the voxel volume and thus the greater the chance of including differing densities, which are then averaged to give the voxel a density on CT. As the final CT image represents all the voxels, thicker sections will have a greater averaging of each voxel, the so-called "partial volume effect".[42] Thinner sections have less density averaging and are therefore better suited for interstitial imaging.

With modern scanners the effective radiation dose for HRCT is the equivalent of 7-14 CXR, depending on whether 10 or 20 mm interspaces are employed[43]. Worldwide annual background radiation is 1–10 mSv with an average of 2.4 mSv[44] i.e. ~50 CXR worth of radiation per annum (1 CXR = 50 μSv). Due to spacing of thin sections, it is not possible to comprehensively evaluate the entire lung parenchyma and, therefore small lesions may be missed. This can be overcome by simultaneous contiguous thick section CT images being taken where necessary.

In SSc patients with a normal CXR, 29% of cases of SSc will have an abnormal thoracic HRCT.[45] When CXR and HRCT are used in SSc to evaluate dyspnoea and/or abnormal pulmonary function tests, the CXR is abnormal in 59% cases whereas the HRCT is abnormal in 88% cases.[46] Overall, HRCT can detect pulmonary abnormalities in 60–90% SSc patients.[37,47]

HRCT may detect co-existent pathologies, which can help explain disparate loss of TLCO relative to lung volumes, for example FASSc and co-existent emphysema. HRCT may obviate the need for biopsy because of a pathognomic HRCT appearance and can direct the surgeon to the most appropriate site for biopsy.

Several HRCT abnormalities may be seen in FASSc[48]: -

- Ground glass (GG) opacification.
- Reticular pattern (fine through to honeycombing).
- Subpleural distribution (especially honeycombing).
- Traction bronchiolectasis.
- Cysts of 1–3 cm diameter.
- Various lines – septal, subpleural, and long (non-septal) parenchymal lines.
- Micronodulation (especially subpleural but also intralobular).

Other non-parenchymal abnormalities may be seen on thoracic HRCT in SSc patients including: -

- Mediastinal lymphadenopathy.[49]
- Pulmonary arterial hypertension.[50]
- Lung cancer.[37]
- Aspiration pneumonia.[51]

Traditionally, GG change on HRCT has been thought to correlate with cellular inflammatory infiltrates and reticular shadowing with fibrosis. GG opacification arises from displacement of air from airspaces, which can occur because of fluid, fibrosis or during expiration. Unlike the CXR, GG on HRCT does not obscure the pulmonary vasculature.[52,53] However, GG may represent fine fibrosis,[54,55] particularly when it is part of a predominantly more reticular pattern. Clues to this include traction bronchiectasis or bronchiolectasis.

HRCT has been used as a predictor of FASSc histology. Wells et al.[56] compared HRCT appearances in 12 FASSc patients with their open lung biopsy appearances. Two grading systems were used, one for HRCT appearances and one for histological appearances. They found a significant ($p < 0.04$) association between grade 4 HRCT appearance (predominantly reticular pattern) and a fibrotic histological appearance, and a significant association between grade 3 HRCT appearance (amorphous parenchymal opacification equal in extent to reticulation) and an inflammatory histological appearance.

Subsequently, the same authors examined the use of HRCT to predict prognosis and response to treatment in FASSc. They reviewed 66 FASSc patients, of whom 36 had confirmatory histology from open lung biopsy.[57] The HRCT appearances were divided into 3 grades (different from those in the earlier study above): grade 1 [GG > reticular pattern]; grade 2 [GG = reticular pattern]; grade 3 [GG < reticular pattern]. They found that, whilst percent predicted FVC was predictive of survival in FASSc ($p < 0.01$), the HRCT appearance did not predict 4-year survival ($p = 0.26$). They also found the duration of dyspnoea in FASSc at the time of HRCT was longer for grade 3 than grade 2 appearances ($p < 0.05$). With treatment, there was a non-significant ($p = 0.10$) improvement in PFT at 1 year in 5/11 (45%) grade 2 and 2/13 (15%) grade 3 FASSc patients. PFT deterioration was commonest in FASSc patients with grade 3 HRCT appearances, although this did not reach statistical significance ($p = 0.14$). Of the 66 patients, 13 had received no treatment prior to HRCT examination. An analysis of this subpopulation revealed that the 3 patients who improved, as judged by PFT, all had grade 2 HRCT appearances initially, although this failed to reach statistical significance ($p = 0.12$).

5.3. DTPA scanning

^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) scanning assesses pulmonary epithelial permeability and hence alveolar-capillary integrity. DTPA is administered by nebuliser and the rate of diffusion from alveoli to the vascular space is measured with a gamma camera. The quicker the DTPA clearance, the greater the pulmonary epithelial permeability, which is thought to be indicative of inflammation. In normal humans, half-time clearance from each lung is approximately 40 min.[58] DTPA clearance is greatly increased in cigarette smokers,[59] as a result of surfactant dysfunction.[59]

DTPA in SSc patients may detect pulmonary involvement in SSc at an earlier stage, even in the presence of normal chest radiology (CXR and HRCT).[60] DTPA clearance has been assessed in SSc patients with no respiratory symptoms and a normal CXR, and was rapid in 6/16 (38%) patients but, of these, 5/6 (83%) had early FASSc on HRCT.[61]

Normal DTPA (>40 min) predicts stable disease but rapid DTPA (<40 min) is not synonymous with disease progression.[62] If DTPA is repeated at 12 months then 2 subgroups emerge: one with sustained fast DTPA clearance who have increased risk of disease progression; and one who revert to normal DTPA clearance, which is associated with a "sustained improvement in respiratory function indices".[53]

6. Bronchoalveolar lavage

Attempts have been made to standardise bronchoalveolar lavage (BAL)[63] but there remains differing definitions of what constitutes "alveolitis" in FASSc.[64–66]

Emerging evidence suggests that the type of granulocytic BAL is important in determining prognosis. Several studies have used BAL neutrophilia as an index of disease activity.[23,64,65] However, this has been challenged by evidence that BAL neutrophilia is no different between FASSc and the more progressive disease, idiopathic pulmonary fibrosis (IPF), once disease extent and functional impairment have been taken into account.[67] In this study, BAL neutrophilia was strongly linked to the extent of reticular fibrotic abnormalities on HRCT.[67] It is therefore likely that BAL neutrophilia is merely a reflection of the extent of fibrosis rather than an implicitly more aggressive phenotype.

However, BAL eosinophilia may have predictive value, independent of any association with disease extent at the time of BAL. In contrast to BAL neutrophilia, BAL eosinophilia is higher in IPF compared to FASSc, when disease extent and functional impairment have been taken into account.[67] BAL eosinophilia is associated with significantly higher mortality in FASSc patients with biopsy proven NSIP.[68]

It has therefore been suggested that BAL neutrophilia occurs in more extensive disease, whereas BAL eosinophilia denotes intrinsically more progressive disease, independent of disease extent.[69]

7. Lung biopsy

Historically, biopsy and histology have been considered the gold standard in the diagnosis of DPLD, although this is now being challenged with the suggestion that it is the most "argentiferous of the silver standards of clinical, radiological and histopathological evaluation".[70]

FASSc should not be diagnosed by bronchoscopic biopsy as specimens are small and there is great scope for sampling error.[71,72] Surgical lung biopsy provides larger biopsy specimens, which are more likely to yield a diagnosis. Open lung biopsy (OLB) has a greater yield than transbronchial biopsy (94% vs 72%)[72] but is generally not repeatable, which makes its use as a measure of disease activity unacceptable.

Video-assisted thoracoscopic surgery is now frequently used for surgical lung biopsy in diffuse lung diseases and has a similar safety and diagnostic efficacy but a reduced operative and hospital stay.[73]

8. Treatment of FASSc

Studies have failed to show any convincing benefit when FASSc patients are treated with corticosteroids[15,16]. Additionally, high dose corticosteroids (>20 mg/day prednisolone) are associated with renal crisis, independent of blood pressure.[17] High dose corticosteroids are therefore not recommended unless there is accelerated disease, in which case the kidneys should be "protected" with Iloprost, which may ameliorate renal vasospasm.[18]

Early studies of cyclophosphamide have shown variable benefits on pulmonary function and survival,[19–23] although the consensus opinion is that cyclophosphamide is the best drug for FASSc.[24] Intravenous cyclophosphamide can result in partial regression of FASSc, as judged by serial PFT[25,26] or serial HRCT.[25,27]

More recently two randomised controlled trials of intravenous cyclophosphamide vs placebo have shown a trend towards stabilisation of pulmonary function in a subset of patients[28] and a small (2.5% predicted) better forced vital capacity (FVC).[29]

Uncontrolled retrospective reviews have shown that azathioprine may help stabilise pulmonary function and improve symptoms in SSc.[30]

Conflict of interest

The authors have no conflict of interest.

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CME section

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Educational questions

1. In systemic sclerosis, which autoantibody is most associated with pulmonary arterial hypertension?
   a. Anti-centromere
   b. Anti-topoisomerase I
   c. Anti-nuclear antibody
   d. Anti-dsDNA
   e. Anti-Ro
2. A patient with systemic sclerosis has normal spirometric and static lung volumes but a reduced gas transfer. What is the most likely explanation?
   a. Pulmonary fibrosis
   b. Cuirasse effect of thoracic skin tightening
   c. Pulmonary vasculopathy
   d. Pleural effusion
   e. Pulmonary haemorrhage
3. Which one of the following is true of DTPA scanning in fibrosing alveolitis due to systemic sclerosis (FASSc)?
   a. Clearance is reduced in cigarette smokers
   b. Fast clearance indicates imminent disease progression
   c. Will be normal if high resolution CT (HRCT) scan is normal
   d. May be fast even in the absence of respiratory symptoms
   e. Must be administered by slow intravenous injection
4. Which one of the following is true of bronchoalveolar lavage (BAL) in fibrosing alveolitis due to systemic sclerosis (FASSc)?
   a. BAL is contra-indicated if lung function abnormal
   b. BAL neutrophilia indicates disease activity
   c. BAL eosinophilia is associated with a higher mortality
   d. BAL eosinophilia is dependent upon disease extent on HRCT
   e. BAL eosinophilia is higher in FASSc than idiopathic pulmonary fibrosis, once adjusted for disease extent and functional impairment
5. Concerning the treatment of FASSc, which one of the following is true?
   a. High dose corticosteroids are needed if co-existent renal disease
   b. Intravenous cyclophosphamide may stabilize lung function
   c. Corticosteroids are contra-indicated if patient on iloprost
   d. Intravenous cyclophosphamide should only be used in diffuse systemic sclerosis
   e. Randomized controlled trials have proven azathioprine to be the drug of choice

References

1. Morrow WJM, Nelson JL, Watts RA, Isenberg DA, Morrow WJM, Nelson JL, et al. *Scleroderma. Autoimmune rheumatic disease*. Oxford: Oxford University Press; 1999.
2. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger Jr TA, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol.* 1988;**15**(2):202–5.
3. Eisenberg H. The interstitial lung diseases associated with the collagen-vascular disorders. *Clin Chest Med* 1982;**3**(3):565–78.
4. Abu-Shakra M, Guillemin F, Lee P. Cancer in systemic sclerosis. *Arthritis Rheum.* 1993;**36**(4):460–4.
5. Alton E, Turner-Warwick M, Black CM, Jayson MIV. *lung involvement in scleroderma. Systemic sclerosis (Scleroderma)*. Chichester: Wiley; 1988.
6. Wigley JEM, Edmunds V, Bradley R. Pulmonary fibrosis in scleroderma. *Br J Dermatol* 1949;**61**:324–7.
7. Pope JE, Lee P, Baron M, Dunne J, Smith D, Docherty PS, et al. Prevalence of elevated pulmonary arterial pressures measured by echocardiography in a multicenter study of patients with systemic sclerosis. *J Rheumatol* 2005;**32**(7):1273–8.
8. Sacks DG, Okano Y, Steen VD, Curtiss E, Shapiro LS, Medsger Jr TA. Isolated pulmonary hypertension in systemic sclerosis with diffuse cutaneous involvement: association with serum anti-U3RNP antibody. *J Rheumatol* 1996;**23**(4):639–42.
9. Launay D, Mouthon L, Hachulla E, Pagnoux C, de Groote P, Remy-Jardin M, et al. Prevalence and characteristics of moderate to severe pulmonary hypertension in systemic sclerosis with and without interstitial lung disease. *J Rheumatol* 2007;**34**(5):1005–11.
10. Morelli S, Barbieri C, Sgreccia A, Ferrante L, Pittoni V, Conti F, et al. Relationship between cutaneous and pulmonary involvement in systemic sclerosis. *J Rheumatol.* 1997;**24**(1):81–5.
11. Tan EM, Feltkamp TE, Smolen JS, Butcher B, Dawkins R, Fritzler MJ, et al. Range of antinuclear antibodies in "healthy" individuals. *Arthritis Rheum.* 1997;**40**(9):1601–11.
12. Steen VD, Powell DL, Medsger Jr TA. Clinical correlations and prognosis based on serum autoantibodies in patients with systemic sclerosis. *Arthritis Rheum.* 1988;**31**(2):196–203.
13. Gilchrist FC, Bunn C, Foley PJ, Lympany PA, Black CM, Welsh KI, et al. Class II HLA associations with autoantibodies in scleroderma: a highly significant role for HLA-DP. *Genes Immun* 2001;**2**(2):76–81.
14. Grassegger A, Pohla-Gubo G, Frauscher M, Hintner H. Autoantibodies in systemic sclerosis (scleroderma): clues for clinical evaluation, prognosis and pathogenesis. *Wien Med Wochenschr* 2008;**158**(1–2):19–28.
15. Dines DE. Pulmonary disease of vascular origin. *Dis Chest* 1968;**54**(1):3–12.
16. Rossi GA, Bitterman PB, Rennard SI, Ferrans VJ, Crystal RG. Evidence for chronic inflammation as a component of the interstitial lung disease associated with progressive systemic sclerosis. *Am Rev Respir Dis* 1985;**131**(4):612–7.
17. Helfrich DJ, Banner B, Steen VD, Medsger Jr TA. Normotensive renal failure in systemic sclerosis. *Arthritis Rheum.* 1989;**32**(9):1128–34.
18. Scorza R, Rivolta R, Mascagni B, Berruti V, Bazzi S, Castagnone D, et al. Effect of iloprost infusion on the resistance index of renal vessels of patients with systemic sclerosis. *J Rheumatol.* 1997;**24**(10):1944–8.
19. Akesson A, Scheja A, Lundin A, Wollheim FA. Improved pulmonary function in systemic sclerosis after treatment with cyclophosphamide. *Arthritis Rheum.* 1994;**37**(5):729–35.
20. Davas EM, Peppas C, Maragou M, Alvanou E, Hondros D, Dantis PC. Intravenous cyclophosphamide pulse therapy for the treatment of lung disease associated with scleroderma. *Clin Rheumatol.* 1999;**18**(6):455–61.
21. Silver RM, Warrick JH, Kinsella MB, Staudt LS, Baumann MH, Strange C. Cyclophosphamide and low-dose prednisone therapy in patients with systemic sclerosis (scleroderma) with interstitial lung disease. *J Rheumatol.* 1993;**20**(5):838–44.
22. Varai G, Earle L, Jimenez SA, Steiner RM, Varga J. A pilot study of intermittent intravenous cyclophosphamide for the treatment of systemic sclerosis associated lung disease. *J Rheumatol.* 1998;**25**(7):1325–9.
23. White B, Moore WC, Wigley FM, Xiao HQ, Wise RA. Cyclophosphamide is associated with pulmonary function and survival benefit in patients with scleroderma and alveolitis. *Ann.Intern.Med* 2000;**132**(12):947–54.
24. Steen VD, Lanz Jr JK, Conte C, Owens GR, Medsger Jr TA. Therapy for severe interstitial lung disease in systemic sclerosis. A retrospective study. *Arthritis Rheum.* 1994;**37**(9):1290–6.
25. Pakas I, Ioannidis JP, Malagari K, Skopouli FN, Moutsopoulos HM, Vlachoyiannopoulos PG. Cyclophosphamide with low or high dose prednisolone for systemic sclerosis lung disease. *J.Rheumatol.* 2002;**29**(2):298–304.
26. Giacomelli R, Valentini G, Salsano F, Cipriani P, Sambo P, Conforti ML, et al. Cyclophosphamide pulse regimen in the treatment of alveolitis in systemic sclerosis. *J.Rheumatol.* 2002;**29**(4):731–6.
27. Griffiths B, Miles S, Moss H, Robertson R, Veale D, Emery P. Systemic sclerosis and interstitial lung disease: a pilot study using pulse intravenous methylprednisolone and cyclophosphamide to assess the effect on high resolution computed tomography scan and lung function. *J.Rheumatol.* 2002;**29**(11):2371–8.
28. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum* 2006;**54**(12):3962–70.
29. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006;**354**(25):2655–66.
30. Dheda K, Lalloo UG, Cassim B, Mody GM. Experience with azathioprine in systemic sclerosis associated with interstitial lung disease. *Clin Rheumatol.* 2004;**23**(4):306–9.
31. Godfrey S, Bluestone R, Higgs BE. Lung function and the response to exercise in systemic sclerosis. *Thorax* 1969;**24**(4):427–34.

32. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;**26**(5):948–68.
33. West J. Restrictive diseases. In: West J, editor. *Pulmonary pathophysiology: the essentials*. 5th ed. Pennsylvania: Williams & Wilkins; 1998. p. 82.
34. Wells AU, Hansell DM, Rubens MB, King AD, Cramer D, Black CM, et al. Fibrosing alveolitis in systemic sclerosis: indices of lung function in relation to extent of disease on computed tomography. *Arthritis Rheum.* 1997;**40**(7):1229–36.
35. Buch MH, Denton CP, Furst DE, Guillevin L, Rubin LJ, Wells AU, et al. Submaximal exercise testing in the assessment of interstitial lung disease secondary to systemic sclerosis: reproducibility and correlations of the 6-min walk test. *Ann Rheum Dis* 2007;**66**(2):169–73.
36. Villalba WO, Sampaio-Barros PD, Pereira MC, Cerqueira EM, Leme Jr CA, Marques-Neto JF, et al. Six-minute walk test for the evaluation of pulmonary disease severity in scleroderma patients. *Chest* 2007;**131**(1):217–22.
37. Arroliga AC, Podell DN, Matthay RA. Pulmonary manifestations of scleroderma. *J Thorac Imaging* 1992;**7**(2):30–45.
38. Taormina VJ, Miller WT, Gefter WB, Epstein DM. Progressive systemic sclerosis subgroups: variable pulmonary features. *AJR Am J Roentgenol.* 1981;**137**(2):277–85.
39. Lomeo RM, Cornella RJ, Schabel SI, Silver RM. Progressive systemic sclerosis sine scleroderma presenting as pulmonary interstitial fibrosis. *Am J Med* 1989;**87**(5):525–7.
40. Israel MS, Harley BJS. Spontaneous pneumothorax in scleroderma. *Thorax* 1956;**11**:113–8.
41. Bhalla M, Silver RM, Shepard JA, McLoud TC. Chest CT in patients with scleroderma: prevalence of asymptomatic esophageal dilatation and mediastinal lymphadenopathy. *AJR Am J Roentgenol.* 1993;**161**(2):269–72.
42. Hansell DM, Armstrong P, Wilson AG, Dee P, Hansell DM. *Technical considerations. Imaging of diseases of the chest*. London: Mosby; 2000.
43. Cushley MJ, Davison AG, du Bois RM, Egan J, Flower CDR, Gibson GJ, et al. The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults. *Thorax* 1999;**54**:S1–30.
44. Radiation UNSCotEoA. Sources and effects of ionizing radiation. Vienna, 2000:111.
45. Schurawitzki H, Stiglbauer R, Graninger W, Herold C, Polzleitner D, Burghuber OC, et al. Interstitial lung disease in progressive systemic sclerosis: high-resolution CT versus radiography. *Radiology* 1990;**176**(3):755–9.
46. Warrick JH, Bhalla M, Schabel SI, Silver RM. High resolution computed tomography in early scleroderma lung disease. *J Rheumatol* 1991;**18**(10):1520–8.
47. Fujita J, Yoshinouchi T, Ohtsuki Y, Tokuda M, Yang Y, Yamadori I, et al. Non-specific interstitial pneumonia as pulmonary involvement of systemic sclerosis. *Ann.Rheum.Dis* 2001;**60**(3):281–3.
48. Wilson AG, Hansell DM, Armstrong P, Wilson AG, Dee P, Hansell DM. *Immunologic diseases of the lung. Imaging of diseases of the chest*. London: Mosby; 2000.
49. Garber SJ, Wells AU, duBois RM, Hansell DM. Enlarged mediastinal lymph nodes in the fibrosing alveolitis of systemic sclerosis. *Br J Radiol.* 1992;**65**(779):983–6.
50. Stupi AM, Steen VD, Owens GR, Barnes EL, Rodnan GP, Medsger Jr TA. Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. *Arthritis Rheum.* 1986;**29**(4):515–24.
51. Silver RM, Miller KS. Lung involvement in systemic sclerosis. *Rheum.Dis Clin North Am* 1990;**16**(1):199–216.
52. Engeler CE, Tashjian JH, Trenkner SW, Walsh JW. Ground-glass opacity of the lung parenchyma: a guide to analysis with high-resolution CT. *AJR Am J Roentgenol.* 1993;**160**(2):249–51.
53. Remy-Jardin M, Remy J, Giraud F, Wattinne L, Gosselin B. Computed tomography assessment of ground-glass opacity: semiology and significance. *J Thorac Imaging* 1993;**8**(4):249–64.
54. Leung AN, Miller RR, Muller NL. Parenchymal opacification in chronic infiltrative lung diseases: CT-pathologic correlation. *Radiology* 1993;**188**(1):209–14.
55. Remy-Jardin M, Giraud F, Remy J, Copin MC, Gosselin B, Duhamel A. Importance of ground-glass attenuation in chronic diffuse infiltrative lung disease: pathologic-CT correlation. *Radiology* 1993;**189**(3):693–8.
56. Wells AU, Hansell DM, Corrin B, Harrison NK, Goldstraw P, Black CM, et al. High resolution computed tomography as a predictor of lung histology in systemic sclerosis. *Thorax* 1992;**47**(9):738–42.
57. Wells AU, Hansell DM, Rubens MB, Cullinan P, Black CM, duBois RM. The predictive value of appearances on thin-section computed tomography in fibrosing alveolitis. *Am Rev Respir Dis* 1993;**148**(4 Pt 1):1076–82.
58. Coates G, O'Brodovich H. Measurement of pulmonary epithelial permeability with 99mTc-DTPA aerosol. *Semin Nucl Med* 1986;**16**(4):275–84.
59. Schmekel B, Bos JA, Khan AR, Wohlfart B, Lachmann B, Wollmer P. Integrity of the alveolar-capillary barrier and alveolar surfactant system in smokers. *Thorax* 1992;**47**(8):603–8.
60. Harrison NK, Glanville AR, Strickland B, Haslam PL, Corrin B, Addis BJ, et al. Pulmonary involvement in systemic sclerosis: the detection of early changes by thin section CT scan, bronchoalveolar lavage and 99mTc-DTPA clearance. *Respir Med* 1989;**83**(5):403–14.
61. Fanti S, De Fabritiis A, Aloisi D, Dondi M, Marengo M, Compagnone G, et al. Early pulmonary involvement in systemic sclerosis assessed by technetium-99m-DTPA clearance rate. *J Nucl Med* 1994;**35**(12):1933–6.
62. Wells AU, Hansell DM, Harrison NK, Lawrence R, Black CM, duBois RM. Clearance of inhaled 99mTc-DTPA predicts the clinical course of fibrosing alveolitis. *Eur Respir J* 1993;**6**(6):797–802.
63. Haslam PL, Baughman RP. Report of ERS task force: guidelines for measurement of acellular components and standardization of BAL. *Eur Respir J* 1999;**14**(2):245–8.
64. Behr J, Vogelmeier C, Beinert T, Meurer M, Krombach F, Konig G, et al. Bronchoalveolar lavage for evaluation and management of scleroderma disease of the lung. *Am J Respir Crit Care Med* 1996;**154**(2 Pt 1):400–6.
65. Silver RM, Miller KS, Kinsella MB, Smith EA, Schabel SI. Evaluation and management of scleroderma lung disease using bronchoalveolar lavage. *Am J Med* 1990;**88**(5):470–6.
66. Witt C, Borges AC, John M, Fietze I, Baumann G, Krause A. Pulmonary involvement in diffuse cutaneous systemic sclerosis: broncheoalveolar fluid granulocytosis predicts progression of fibrosing alveolitis. *Ann Rheum Dis* 1999;**58**(10):635–40.
67. Wells AU, Hansell DM, Haslam PL, Rubens MB, Cailes J, Black CM, et al. Bronchoalveolar lavage cellularity: lone cryptogenic fibrosing alveolitis compared with the fibrosing alveolitis of systemic sclerosis. *Am J Respir Crit Care Med.* 1998;**157**(5 Pt 1):1474–82.
68. Bouros D, Wells AU, Nicholson AG, Colby TV, Polychronopoulos V, Pantelidis P, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. *Am J Respir Crit Care Med* 2002;**165**(12):1581–6.
69. Latsi PI, Wells AU. Evaluation and management of alveolitis and interstitial lung disease in scleroderma. *Curr.Opin.Rheumatol.* 2003;**15**(6):748–55.
70. Wells AU. Histopathologic diagnosis in diffuse lung disease: an ailing gold standard. *Am J Respir Crit Care Med.* 2004;**170**(8):828–9.
71. Fechner RE, Greenberg SD, Wilson RK, Stevens PM. Evaluation of transbronchial biopsy of the lung. *Am J Clin Pathol.* 1977;**68**(1):17–20.
72. Wall CP, Gaensler EA, Carrington CB, Hayes JA. Comparison of transbronchial and open biopsies in chronic infiltrative lung diseases. *Am Rev Respir Dis* 1981;**123**(3):280–5.
73. Mouroux J, Clary-Meinesz C, Padovani B, Perrin C, Rotomondo C, Chavaillon JM, et al. Efficacy and safety of videothoracoscopic lung biopsy in the diagnosis of interstitial lung disease. *Eur J Cardiothorac Surg* 1997;**11**(1):22–4. p. 22–6.